STATUS OF CLAIMS

Claims 1, 3-8, 17-19, 34, 38 and 49-72 are pending. All the previously pending claims, claims 1-8, 17-19, 34, 38 and 48-59, have been rejected in the Office Action dated October 20, 2004.

STATUS OF AMENDMENTS

Claims 1, 34, 38 and 50 have been amended. Claims 2 and 48 have been cancelled and incorporated into claims 1 and 34, respectively. New claims 60-72 have been added. No new matter has been added.

SUMMARY OF CLAIMED SUBJECT MATTER

The present invention includes a combination of a crystallizable polymer and an amorphous polymer.[1] The amorphous polymer may provide a slow release of an entrained bioactive agent at a constant or nearly constant rate, often referred to as zero-order kinetics. Specification, page 1, lines 13-15 and page 19, lines 21-24. The crystallizable polymer may provide rapid release of an entrained bioactive agent during crystallization, referred to as non-zero-order kinetics. Specification, page 19, lines 5-6.

The ratio of the crystallizable polymer to the amorphous polymer in a specific composition may be altered to provide the desired profile of non-zero-order and zero-order release for the bioactive agent. Specification, page 3, lines 28-29. For example, the ratio chosen may provide a rapid release at the desired time point provided by the crystallizable polymer in combination with a substantially longer,

[1] A "crystallizable polymer" assumes a "semi-crystalline" order when crystallized. All polymers capable of adopting a semi-crystalline order are crystallizable. Amorphous polymers cannot assume a semi-crystalline order and are not crystallizable.

but lower concentration, release provided by the amorphous polymer. Specification, page 19, lines 20-30.

Independent claim 1 now provides an injectable composition for the controlled release of a bioactive agent. Specification, page 16, lines 14-17 and page 17, lines 15-28. The composition includes a biodegradable crystallizable polymer, a biodegradable amorphous polymer, a biocompatible solvent and a bioactive agent. Specification, page 3, lines 27-30 and page 5, lines 1-3, 19-20. The biocompatible solvent has a miscibility with water less than 7 percent by weight. Specification, page 5, lines 23-25.

Independent claim 34 now provides a method of administering a bioactive agent, including inserting an injectable composition for the controlled release of a bioactive agent into an organism. Specification, page 16, lines 14-17 and page 17, lines 15-28. The composition includes a biodegradable crystallizable polymer, a biodegradable amorphous polymer, a biocompatible solvent, and a bioactive agent. Specification, page 3, lines 27-30 and page 5, lines 1-3, 19-20. The biocompatible solvent has a miscibility with water less than 7 percent by weight. Specification, page 5, lines 23-25.

Independent claim 38 now provides a method of making an injectable composition for administering a bioactive agent. Specification, page 16, lines 14-17 and page 17, lines 15-28. The method includes combining ingredients, where the ingredients include a biodegradable crystallizable polymer, a biodegradable amorphous polymer, a biocompatible solvent, and a bioactive agent. Specification, page 3, lines 27-30 and page 5, lines 1-3, 19-20. The biocompatible solvent has a miscibility with water less than 7 percent by weight. Specification, page 5, lines 23-25.

GROUNDS OF REJECTION TO BE REVIEWED

The issues to be decided in this response are as follows:

Whether claims 1-6, 34, 38, 48-52, 58 and 59 are anticipated under 35 U.S.C. § 102(a) over PCT Application Publication No. WO 00/57852 to Dang et al. (*Dang*).

Whether claims 1, 2, 5-7, 17, 18, 34, 38, 48, 51-53, 55, 56, 58 and 59 are anticipated under 35 U.S.C. § 102(b) over U.S. Patent No. 5,525,646 to Lundgren et al. (*Lundgren*).

Whether claims 1-3, 5, 34, 38, 48, 49, 51, 58 and 59 are obvious under 35 U.S.C. § 103(a) over U.S. Patent No. 6,432,438 to Shukla (*Shukla*) in view of PCT Application Publication No. WO 88/07366 to Bateman et al. (*Bateman*).

Whether claims 1-3, 5, 34, 38, 48, 49, 51, 58 and 59 are obvious under 35 U.S.C. § 103(a) over *Shukla* in view of *Lundgren*.

Whether claims 1-19, 34, 38 and 48-59 are obvious under 35 U.S.C. § 103(a) over U.S. Patent No. 6,432,438 to Brodbeck et al. (*Brodbeck*) in view of *Lundgren*.

ARGUMENT

A. *Dang* Does Not Disclose The Claimed Combination Of Polymers In Combination With A Biocompatible Solvent Having A Miscibility With Water Less Than 7 Percent By Weight.

To anticipate a claim, a reference must disclose each and every element of the claim. MPEP § 2131. The rejection of claims 1-6, 34, 38, 48-52, 58 and 59 as anticipated by *Dang* has been obviated by appropriate amendment. *Dang* does not disclose a composition including a biodegradable crystallizable polymer, a biodegradable amorphous polymer, and a biocompatible solvent having a miscibility with water less than 7 percent by weight.

Dang discloses a combination of a biodegradable poly(phosphoester) and an antineoplastic agent for treatment of a tumor, that can be administered to the tumor by injection. *Dang*, page 13, lines 12-19. The poly(phosphoester) can be blended with other biocompatible polymers. *Dang*, page 38, line 21 through page 39, line 12. The reference discloses that organic solvents may be used for making the polymers and for mixing the polymer with the antineoplastic agent prior to formation of the final therapeutic composition. *Dang*, page 25, line 30 through page 26, line 12, and page 40, lines 1-9, 31-36.

Dang does not disclose a combination of a biodegradable crystallizable polymer, a biodegradable amorphous polymer, and a biocompatible solvent having a miscibility with water less than 7 percent by weight. The reference is silent regarding whether the poly(phosphoester) is amorphous or crystallizable. The discussion of polymer morphology is directed to other monomeric units that may have varying degrees of crystallization, and that may be incorporated into the poly(phosphoester). *Dang*, page 27, lines 7-13. The listing of polymers that could be blended with the poly(phosphoester) does not include any teaching of selecting a poly(phosphoester) and a non-poly(phosphoester) such that one of the polymers is amorphous and one is crystallizable. Thus, the reference does not disclose, teach or

suggest the combination of a biodegradable crystallizable polymer and a biodegradable amorphous polymer.

Dang also is silent regarding the water-miscibility of any solvents used to prepare or process the poly(phosphoester). Moreover, the reference teaches away from the use of any solvent in an injectable mixture, specifically teaching that there should not be significant amounts of saline or of a water-immiscible organic solvent. *Dang*, page 2, lines 1-5; page 25, line 30 through page 26, line 2; and page 40, lines 1-9 and 29-35. Thus, the reference does not disclose, teach or suggest the combination of any polymer composition with a biocompatible solvent having a miscibility with water less than 7 percent by weight.

Independent claims 1, 34 and 38 as amended each include a combination of a biodegradable crystallizable polymer, a biodegradable amorphous polymer, and a biocompatible solvent having a miscibility with water less than 7 percent by weight. *Dang* does not disclose, teach or suggest the combination of a biodegradable crystallizable polymer and a biodegradable amorphous polymer, nor does the reference disclose, teach or suggest the combination of these polymers with a biocompatible solvent having a miscibility with water less than 7 percent by weight. Accordingly, claims 1, 3-6, 34, 38, 49-52, 58 and 59 are neither anticipated by, nor obvious over, the cited reference. Applicants respectfully request that this rejection be withdrawn.

B. *Lundgren* Does Not Disclose An Injectable Composition For Administration Of A Bioactive Agent.

The rejection of claims 1, 2, 5-7, 17, 18, 34, 38, 48, 51-53, 55, 56, 58 and 59 as anticipated by *Lundgren* has been obviated by appropriate amendment. *Lundgren* does not disclose an injectable composition for administration of a bioactive agent.

Lundgren discloses biodegradable compositions for use in tissue regeneration, where the composition is both malleable and dimensionally stable. *Lundgren*, col. 4, lines 60-67. The reference describes a malleable composition as having a shape that "can be adapted to the shape of the region to be covered, often in a three-dimensional fashion." *Lundgren*, col. 1, lines 33-44. The reference describes a dimensionally stable material as having a shape that "can be maintained over a certain period of time." *Lundgren*, col. 1, lines 45-51. The malleable and dimensionally stable compositions can contain an amorphous polymer in combination with small amounts of a crystallizable polymer and a plasticizer. *Lundgren*, col. 5, lines 33-42 and col. 6, line 53 through col. 7, line 33. Administration of the compositions involves forming the composition into the desired shape, and surgically inserting the shaped composition into the patient. *Lundgren*, col. 5, lines 6-14 and col. 10, lines 34-44.

There is no disclosure in *Lundgren* of an injectable composition. The biodegradable compositions of the reference are expressly in a malleable and dimensionally stable form. The disclosed compositions are not capable of being administered by injection. As noted in Applicants' specification, an injectable composition preferably has a viscosity low enough to provide for flow through an 18-20 gauge needle. Specification, page 16, lines 14-19.

Independent claims 1, 34 and 38 as amended each include an injectable composition. *Lundgren* does not disclose, teach or suggest an injectable composition. Accordingly, claims 1, 5-7, 17, 18, 34, 38, 51-53, 55, 56, 58 and 59 are neither anticipated by, nor obvious over, the cited reference. Applicants respectfully request that this rejection be withdrawn.

C. The Cited References Fail To Render Obvious Under 35 U.S.C. § 103 An Injectable Composition Including The Claimed Combination Of Polymers And A Biocompatible Solvent

1. The combination of *Shukla* with *Bateman* would change the principle of operation of *Shukla*.

The rejection of claims 1-3, 5, 34, 38, 48, 49, 51, 58 and 59 as obvious over *Shukla* in view of *Bateman* is respectfully traversed. Combining the teachings of the tablet formulation of *Bateman* with the injectable vehicle of *Shukla* would change the principle of operation of *Shukla*.

Shukla discloses a biodegradable vehicle for filling cavities or tissues in a patient. *Shukla*, col. 1, lines 9-14. The vehicle contains a biodegradable polymer and a plasticizer, and can be formulated to provide a "free-flowing viscous liquid, a gel or a paste." *Shukla*, col. 3, lines 52-54 and col. 4, lines 5-9. The reference discloses that a solvent may be used for combining the polymer and the plasticizer, but that this solvent is removed in order to form the final vehicle composition. *Shukla*, col. 4, line 64 through col. 5, line 13, and col. 5, lines 41-52. When the biodegradable vehicle is used for delivery of a biologically active substance, the biologically active substance is kept separate from the vehicle until just prior to the administration of the composition, in order to maintain the stability of the biologically active substance. *Shukla*, col. 2, lines 48-56; col. 6, lines 37-57; and Figure 1b.

Bateman discloses a solid tablet formulation for controlled release of an active ingredient, containing poly(vinyl alcohol) or a copolymer containing monomeric units derived from vinyl alcohol. *Bateman*, page 5, lines 14-26. The tablets are administered orally or by application to agricultural fields. *Bateman*, page 1, lines 9-17; page 19, lines 29-33; and Examples 7-9. Blends of crystalline poly(vinyl alcohol) with an amorphous poly(vinyl alcohol) or a copolymer

containing monomeric units derived from vinyl alcohol can provide a range of release characteristics. *Bateman*, page 7, line 25 through page 8, line 5.

Independent claims 1, 34 and 38 as amended each include a combination of a biodegradable crystallizable polymer, a biodegradable amorphous polymer, and a biocompatible solvent having a miscibility with water less than 7 percent by weight. The combination of the teachings of *Bateman* and *Shukla* in an attempt to provide these claim elements would be improper, as such a combination would change the principle of operation of *Shukla*. The biodegradable vehicle of *Shukla* provides for filling cavities or tissues in a patient, and is combined with a biologically active substance just prior to administration. The stabilization of the biologically active substance in a container separate from the biodegradable vehicle is critical to the successful use of the vehicle for controlled release of the substance. In contrast, the teaching of *Bateman* regarding the use of blends of amorphous and crystallizable polymers for controlled release is limited to solid tablet formulations, in which the active ingredient must be present when the polymers are blended and pressed into a tablet. An attempt to incorporate the tablet formulations of *Bateman* into the biodegradable vehicle of *Shukla* would provide a composition containing the biologically active substance at the time the formulation was initially prepared. As noted in MPEP § 2143.01, if the proposed modification or combination of the references would change the principle of operation of the reference being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. Accordingly, claims 1, 3, 5, 34, 38, 49, 51, 58 and 59 are not obvious over the cited references. Applicants respectfully request that this rejection be withdrawn.

2. *Lundgren* teaches away from the compositions of *Shukla*.

The rejection of claims 1-3, 5, 34, 38, 48, 49, 51, 58 and 59 as obvious over *Shukla* in view of *Lundgren* is respectfully traversed. The disclosure of *Lundgren* teaches away from the use of injectable vehicles as disclosed in *Shukla*.

Shukla discloses a biodegradable vehicle for filling cavities or tissues in a patient, and has been described above. The plasticizer component of the vehicle functions to improve the flow of the polymer, making the polymer less solid and more flexible. *Shukla* teaches the use of high concentrations of plasticizer, so as to form a composition that is a free-flowing viscous liquid, a gel or a paste. *Shukla*, col. 4, lines 5-39.

Lundgren discloses biodegradable compositions for use in tissue regeneration, and has been described above. The biodegradable compositions are both malleable and dimensionally stable, having a shape that can be maintained over a certain period of time. *Lundgren* teaches that these mechanical properties are a requirement for the compositions to be used for tissue regeneration, and that dimensional stability is important for the duration of the healing process. *Lundgren*, col. 1, lines 27-32 and 45-51.

Independent claims 1, 34 and 38 as amended each include an injectable composition for administration of a bioactive agent. *Lundgren* teaches away from the injectable vehicles of *Shukla*, stating that compositions lacking dimensional stability are unsatisfactory for tissue regeneration. As noted in MPEP § 2145(X)(D)(2), references cannot be combined where a reference teaches away from their combination. Accordingly, claims 1, 3, 5, 34, 38, 49, 51, 58 and 59 are not obvious over the cited references. Applicants respectfully request that this rejection be withdrawn.

3. *Lundgren* teaches away from the compositions of *Brodbeck.*

The rejection of claims 1-19, 34, 38 and 48-59 as obvious over *Brodbeck* in view of *Lundgren* is respectfully traversed. The disclosure of *Lundgren* teaches away from the use of viscous gels as disclosed in *Brodbeck*.

Brodbeck discloses a combination of a biocompatible polymer and a biocompatible solvent for controlled delivery of a beneficial agent. *Brodbeck*, col. 8, lines 36-41. The composition can be a viscous gel, and may be modified to be less viscous in order to administer the composition through a needle. *Brodbeck*, col. 9, lines 8-13.

Lundgren discloses biodegradable compositions for use in tissue regeneration, and has been described above. The biodegradable compositions are both malleable and dimensionally stable, having a shape that can be maintained over a certain period of time. *Lundgren* teaches that these mechanical properties are a requirement for the compositions to be used for tissue regeneration, and that dimensional stability is important for the duration of the healing process.

Independent claims 1, 34 and 38 as amended each include an injectable composition for administration of a bioactive agent. *Lundgren* teaches away from the viscous gels of *Brodbeck*, stating that compositions lacking dimensional stability are unsatisfactory for tissue regeneration. As noted in MPEP § 2145(X)(D)(2), references cannot be combined where a reference teaches away from the combination. Accordingly, claims 1, 3-19, 34, 38 and 49-59 are not obvious over the cited references. Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

In conclusion, all of the grounds raised in the present Office Action for rejecting the application are believed to be overcome or rendered moot based on the remarks above. Thus, it is respectfully submitted that all of the presently presented claims are in form for allowance, and such action is requested. Should the Examiner feel a discussion would expedite the prosecution of this application, the Examiner is kindly invited to contact the undersigned at (312) 876-1400.

Respectfully submitted,

Dated: March 18, 2005

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